

Remarks

Applicants have amended claims 1, 8, 16 and 17 to make explicit that which was implicit, namely that the claims are directed to enriching fetal nucleic acid regions in the maternal plasma sample. Support for the amendments can be found throughout the specification. Accordingly, no new matter has been introduced by the amendments and their entry is respectfully requested.

Applicants respectfully request reconsideration of the rejections as discussed in detail below.

The method of the present invention is based upon the novel discovery that by digesting a substantial amount of the maternal nucleic acid in a sample taken from a pregnant mother, one can more reliably amplify fetal nucleic acids present in the sample. This is accomplished by using methylation sensitive enzymes to substantially destroy the maternal nucleic acids from the sample. After the relative amount of fetal DNA has been thereby increased relative to the remaining maternal sample, alterations in the fetal DNA can be detected with significantly improved accuracy.

The Examiner rejected claims 16 and 17 under 35 U.S.C. §102(b) as allegedly being anticipated over U.S. Patent No. 6,927,028 to Yuk Ming Dennis Lo and Lit Man Poon ("Lo patent").

Applicants respectfully disagree and submit that the rejection should be withdrawn for the following reasons.

Applicants first note that the goal of examination is to **clearly articulate any rejection** early in the prosecution process so that the applicant has the opportunity to provide evidence of patentability and otherwise reply completely at the earliest opportunity (MPEP 706). Further, in rejecting claims for want of novelty or for obviousness, the examiner must cite the best references at his or her command. When a reference is complex or shows or describes inventions other than that claimed by the applicant, the particular part relied on must be designated as nearly as practicable. The pertinence of each reference, if not apparent, must be clearly explained and each rejected claim specified. 37 C.F.R. 1.104(c)(2).

Applicants respectfully submit that the Examiner does not provide any analysis as to why the Lo patent allegedly anticipates claims 16 and 17.

The Lo patent fails to teach an enrichment step, thus, there is no anticipation. The Lo patent states that DNA species can be differentiated by observing epigenetic differences, such as methylation differences, in the DNA species (see, e.g., abstract, lines 6-8). This is not what claims 16 and 17 are directed to. Step (b) of both claim 16 and 17 requires selectively treating the sample **to enrich the sample for at least one fetal nucleic acid region**.

Lo describes that “DNA species are differentiated by **observing epigenetic differences**” (see, e.g., col. 2, lines 18-21, emphasis added). Although Lo describes that one can detect fetal nucleic acids in the maternal sample, there is nothing in Lo that teaches or suggests that during this process, one enriches the fetal nucleic acid by substantially reducing the maternal nucleic acid. All Lo describes is that the “methods provide for detecting fetal DNA in a maternal sample by differentiating the fetal DNA from the maternal DNA based upon epigenetic markers such as differences in DNA methylation” (see, e.g., col. 2, lines 52-56). Therefore, Lo only contemplates **detecting** differential methylation, **not utilizing differential methylation to enrich** fetal nucleic acids in a maternal nucleic acid sample to achieve improved detection of fetal nucleic acids.

As explained in paragraph [012] of the present specification, and required by the claims the present method increases the relative amount of fetal nucleic acid in a maternal plasma sample.

Accordingly, Applicants respectfully submit that the rejection of claims 16 and 17 under 35 U.S.C. §102(b) over Lo is improper and should be withdrawn.

The Examiner also rejected claims 1-14 under 35 U.S.C. § 103(a) as allegedly obvious over the combination of the Lo patent and a U.S. Patent No. 7,348,139 to Herman et al. (“Herman patent”). Specifically, the Examiner alleged that

The Examiner contended that

“claims 1-15 are drawn to method for prenatal diagnosis of chromosomal abnormality using maternal serum or plasma as the source of DNA, the method comprising detecting differential DNA methylation between fetus and mother,

wherein the differential methylation is detected using a methyl-sensitive enzyme that digests only unmethylated DNA.” (Page 4 of the Office Action dated June 11, 2008)

However, this is not what is claimed. Step b of claim 1, for example, reads “b) **digesting DNA from said plasma sample with an enzyme that selectively and substantially completely digests the maternal DNA** to obtain a DNA sample enriched for fetal DNA regions.” Nothing in Lo teaches a step of reducing or **destroying the maternal DNA to enrich the fetal DNA** in the maternal sample.

The Examiner acknowledges that Lo does not teach a methyl-sensitive enzyme that digests only unmethylated DNA.

The Herman patent does not teach such a method step. All Herman teaches is that “methylation can be detected by contacting a nucleic acid molecule, which includes all or a portion of a CpG island of the SOCS/CIS gene sequence, with a methylation sensitive restriction endonuclease.” Herman only talks about detecting methylation differences, not using them to enrich fetal DNA in a maternal sample which contains a lot of maternal DNA and very little of fetal DNA.

The Examiner alleged that “one of ordinary skill in the art would have been motivated to use the claimed invention since using a methyl-sensitive enzyme that digests only unmethylated DNA seems to be an art-equivalent method of detecting methylation status of DNA.”

However, this is not what is claimed. The claims are not directed to detection of methylation differences. The claims are directed to using methylation differences to enrich the fetal DNA over the maternal DNA.

There is nothing in either Lo or Herman that teaches or suggests such a method.

Accordingly, the rejection of claims 1-14 under 35 U.S.C. §103(a) over Lo in view of Herman is improper and should be withdrawn.

In view of the foregoing, Applicants respectfully submit that all claims are in condition for allowance. Early and favorable action is requested.

In the event that any additional fees are required, the Commissioner is hereby is authorized to charge our deposit account No. 50-0850. Any overpayments should also be deposited to said account.

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Respectfully submitted,

Customer No.: 50607

/Leena H. Karttunen/
Ronald I. Eisenstein (Reg. No. 30,628)
Leena H. Karttunen (Reg. No. 60,335)
Nixon Peabody LLP
100 Summer Street
Boston, MA 02110-2131
(617) 345-6054 / 1367